

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 81331-209	FOR FURTHER ACTION	See item 4 below
International application No. PCT/CA2005/000108	International filing date (<i>day/month/year</i>) 27 January 2005 (27.01.2005)	Priority date (<i>day/month/year</i>) 27 January 2004 (27.01.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant THE HOSPITAL FOR SICK CHILDREN		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 <i>bis</i> .1(a).																								
2.	This REPORT consists of a total of 9 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																								
3.	<p>This report contains indications relating to the following items:</p> <table style="width: 100%;"> <tr> <td style="width: 10%; text-align: center;"><input checked="" type="checkbox"/></td> <td style="width: 30%;">Box No. I</td> <td style="width: 60%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input type="checkbox"/>	Box No. II	Priority	<input checked="" type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input checked="" type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input checked="" type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input checked="" type="checkbox"/>	Box No. VIII	Certain observations on the international application
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4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44 <i>bis</i> .3(c) and 93 <i>bis</i> .1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44 <i>bis</i> .2).																								

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Date of issuance of this report 27 July 2006 (27.07.2006)
Facsimile No. +41 22 338 82 70	Authorized officer <div style="text-align: center; font-weight: bold;">Athina Nickitas-Etienne</div> e-mail: pt04@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

REC'D 02 JUN 2005

WIPO

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:
SMART & BIGGAR
Box 11560 Vancouver Centre
2200 - 650 W. Georgia Street
VANCOUVER, British Columbia
Canada, V6B 4N8

Date of mailing 24 May 2005 (24-05-2005)
(day/month/year)

Applicant's or agent's file reference
81331-209

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/CA2005/000108

International filing date (day/month/year)
27 January 2005 (27-01-2005)

Priority date (day/month/year)
27 January 2004 (27-01-2004)

International Patent Classification (IPC) or both national classification and IPC
IPC (7): C12N-5/00 and A61K-35/36

Applicant
THE HOSPITAL FOR SICK CHILDREN ET AL

1. This opinion contains indications relating to the following items :

- | | |
|--|---|
| <input checked="" type="checkbox"/> Box No. I | Basis of the opinion |
| <input type="checkbox"/> Box No. II | Priority |
| <input checked="" type="checkbox"/> Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input checked="" type="checkbox"/> Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement. |
| <input checked="" type="checkbox"/> Box No. VI | Certain documents cited |
| <input type="checkbox"/> Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of :

☐ the entire international application

☐ claim Nos.

because:

☐ the said international application, or the said claim Nos. 3-25
relate to the following subject matter which does not require an international preliminary examination (*specify*) :

Although claims 3-25 encompass methods of medical treatment of the human/animal body which this Authority is not required to examine under Rules 67.1(iv) of the PCT, a written opinion has been established on the basis of the alleged effects of the stem cells referred to therein.

☐ the description, claims or drawings (*indicate particular elements below*) or said claim Nos.
are so unclear that no meaningful opinion could be formed (*specify*) :

☐ the claims, or said claims Nos. are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the
Administrative Instructions in that :

the written form ☐ has not been furnished
☐ does not comply with the standard

the computer readable form ☐ has not been furnished
☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the
technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. IV **Lack of unity of invention**

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has :

☐ paid additional fees

☐ paid additional fees under protest

☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with

☒ not complied with for the following reasons :

There is no single inventive link between claims belonging to groups I, II and III.

Group I: Claims 1-25 are directed to a method of producing a population of at least ten cells and methods of inducing hair growth;

Group II: Claims 26-52 are directed to a kit comprising multipotent stem cells capable of inducing hair growth and a method of making hair follicles;

Group III: Claims 53-63 are directed to a method for regenerating skin in a mammal by providing to said mammal a population of cells.

The broad claims belonging to groups II and III do not specify that the multipotent stem cells are multipotent follicle stem cells. Further, the stem cells of claims belonging to groups I and II do not have the same applications as the stem cells of claims belonging to group III. Finally because neither follicle stem cells or the multipotent stem cells appear to be novel, there is no single inventive link between claims of groups I-III.

4. Consequently, this opinion has been established in respect of the following parts of the international application :

☐ all parts

☒ the parts relating to claim Nos. 1-25

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims <u>21</u>	YES
	Claims <u>1-20 and 22- 25</u>	NO
Inventive step (IS)	Claims <u>21</u>	YES
	Claims <u>1-20 and 22-25</u>	NO
Industrial applicability (IA)	Claims <u>1-25</u>	YES
	Claims <u>None</u>	NO

2. Citations and explanations :

D1: TOMA, J. G. et al. Isolation of multipotent adult stem cells from the dermis of mammalian skin. Nature Cell Biology. 2001, vol 3, pp 778-784

D2: US20030077823 A1 (LINGNA, L. & MENG, Y.) Nestin-expressing hair follicle stem cells. April 24, 2003

D3: WO03/010243 A2 (Toma, J. G. et al.) Multipotent stem cells from peripheral tissues and uses thereof. February 6, 2003

D4: WO01/53461 A1 (Toma, J. G. et al.) Multipotent neural stem cells from peripheral tissues and uses thereof. July 26, 2001.

Claims 1 and 2 are directed to a method for producing a population of multipotent stem cells and claims 3-25 are directed to methods for inducing hair growth using either multipotent stem cells (claim 3 and dependent claims) or hair follicle cells (claim 4 and dependent claims) that differentiated from multipotent stem cells.

Novelty and Inventive Step

Claims 1, 2 and 5-20 lack novelty under PCT Article 33(2) as being anticipated by D3 or D4. D3 and D4 disclosed a method for isolating multipotent stem cells from a hair follicle or from dermal papillae by subjecting skin pieces of a mouse or a human to mechanical dissociation and further digestion with trypsin. D3 and D4 also disclosed that many of the cells produced from said tissue adhered to plastic while other cells floated and proliferated to generate larger spheres of cells that produced nestin, a marker for neural stem cells. Successive cultures on plastic eliminate the plastic adherent cells and enrich for floating cells that produce nestin. Although skin derived precursor stem cells produce the neural marker, nestin, they do not produce the p75 neurotrophin receptor, a marker of neural crest stem cells. D3 and D4 also disclosed that said skin precursors can differentiate into cells of both neuroectodermal and mesodermal lineage including neurons, glia, smooth muscle cells and adipocytes. Because the cells disclosed by D3 and D4 are skin derived precursor stem cells that can be isolated from hair follicles, said cells inherently do not express c-kit, tryp-1, DCT, MBP, P0, SOX10 markers and are capable of differentiating into hair follicles as described on page 5 line 20 to page 6 line 2 of the description of the present application. Finally D3 and D4 disclosed that isolated skin derived precursor stem cells can be transfected with a heterologous gene that encodes for a therapeutic protein.

Claims 1, 2, 5-12 and 14-17 lack novelty under PCT Article 33 (2) as being anticipated by D1. D1 disclosed a method for isolating multipotent stem cells from from dermal papillae by using the same procedure as described in D3 or D4. D1 also disclosed that the cells which do not adhere to plastic floated and proliferated to generate larger spheres and that after 3-4 weeks of passaging, purified populations of "floating cells" were obtained and named skin-derived precursors stem cells. Although skin derived precursor stem cells produced the neural marker, nestin, they do not produce the p75 neurotrophin receptor, a marker of neural crest stem cells.

continued in supplemental box.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/CA2005/000108

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted :

The abstract does not comply with PCT Rule 8.1 because it fails to indicate the utility of the invention and also fails to reflect the particular subject matter of claims 1-25.

Box No. VIII **Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

The following defects in the form or contents of the international application have been noted:

Claim 1 does not comply with PCT Article 6. Step b) does not define conditions under which multipotent stem cells grow and proliferate non-adherently whereby at least 25 % of the cells that are not multipotent stem cells die or adhere to the culture substrate.

Claim 3 does not comply with PCT Article 5. Said claim is directed to a method for inducing hair growth but applicant only defines the step of providing multipotent stem cells capable of producing hair follicle cells. Therefore the claim does not define all the essential steps of said method.

Claim 4 does not comply with PCT Article 5. Said claims are directed to a method for inducing hair growth but applicant only defines the step of providing hair follicle cells that have differentiated from multipotent stem cells. Therefore the claim does not define all the essential steps of said method.

Claims 9, 10, 29, 37, 38, 48, 59 and 67 do not comply with PCT Article 6 because it is not clear what applicant means by "measurable levels".

Claim 14 does not comply with PCT Article 6 because it is not clear what applicant means by "appropriate conditions".

Claim 20 does not comply with PCT Article 6 because there is no antecedent for the term "gene".

Claim 23 does not comply with PCT Article 6 because it is not clear what applicant means by "immunologically similar".

Claims 24, 31, 39 and 50 do not comply with PCT Article 6 because it is not clear what applicant means by "reduced amount".

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

D1 also disclosed that said skin precursors can differentiate into cells of both neuroectodermal and mesodermal lineage including neurons, glia, smooth muscle cells and adipocytes.

Claims 3, 4, 8-18 and 22- 25 lack novelty under PCT Article 33(2) as being anticipated by D2. D2 disclosed a method for isolating nestin producing hair follicle stem cells from an adult mouse and also disclosed that said cells could be implanted into a mammal for skin replacement or to treat hair loss. D2 also disclosed that hair follicle stem cells differentiate into neurons, astrocytes, smooth muscle cells and adipocytes.

Because claims 1-20 and 22-25 are anticipated by documents D1-D4 they are considered to lack an inventive step. Claim 21 is considered novel and inventive because no prior art teaches the subject matter of said claim.

Industrial Applicability

Claims 1-2 appear to define the subject matter that has industrial applicability under Article 33(4) of the PCT, based on the utility of the claimed subject matter for isolating stem cells from hair follicles.

For the assessment of claims 3-25 on the question of whether or not they define subject matter that has industrial applicability no unified criteria exists in the PCT. Further, the patentability of said claims can depend upon their formulation . Although the methods *per se* defined in claims 3-25 relate to subject matter which this Authority is no obliged to examine under Rule 67.1 (iv) of the PCT, the use of the stem cells referred to therein for inducing hair growth appears to represent subject matter that has industrial applicability.